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PS4207

A process for preparing novel chemotherapeutically active 5,8-dimethoxy-2,3-di-(4'-substituted aminomethylphenyl) quinoxaline derivatives and pharmaceutically acceptable salts thereof.

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The following specification describes the nature of this invention.

PRICE: TWO RUPEES

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The present invention relates to novel 5,8-dimethoxy-2,3-di-(4'-substituted aminomethyl-phenyl)quinoxalinee and pharmaceutically acceptable salts thereof, processes for their preparation and their chemotherapeutic properties.

Novel 5,8-dimethoxy-2,3-di(4'-substituted aminomethyl-phenyl) quinoxalines of the invention are presented by the formula 1 of the accompanying drawings, wherein R_1 and R_2 which may be same or different stand for hydrogen, C_1-C_6 alkyl group, for example methyl, ethyl, propyl, hydroxy alkyl, for example hydroxy ethyl, acyl or substituted acyl, for example acetyl or dichloroacetyl, alkene for example allyl; R_1 and R_2 together with the nitrogen to which they are attached form a heterocycle containing one or more hetero atom(s) and is optionally substituted by an alkyl, aralkyl, carboxyalkyl or aryl group which is optionally substituted with substituents such as halogen, hydroxy, alkoxy, alkyl and substituted alkyl groups.

Preferred compounds of the invention are the quinoxalines of the formula I, wherein R_1 and R_2 stand for C_1-C_4 alkyl groups for example methyl, ethyl, isopropyl.

Examples of heterocycles are piperazine, piperidine, pyrrolidine, morpholine or homopiperidine.

Particularly preferred compounds of the invention are 2,3-Di(4-N-methylpiperazinomethyl phenyl)-5,8-dimethoxy quinoxaline.

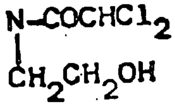
2,3-Di(4-piperidinomethyl phenyl)-5,8-dimethoxy quinoxaline.

2,3-Di(4-pyrrolidinomethyl phenyl)-5,8-dimethoxy quinoxaline.

2,3-Di(4-homopiperidinomethyl phenyl)-5,8-dimethoxy quinoxaline.

Some, 5,8-dimethoxy-2,3-di(4'-substituted aminomethyl phenyl)-quinoxalines of the invention are listed in the following Table I :

TABLE 1

See Fig.1 of the accompanying drawings	m.p. °C
$N(C_2H_5)_2 - H_2O$	78-80
$N(CH_2CH{=}CH_2)_2$	133-35
 $N(COCHCl_2)(CH_2CH_2OH)$	127
See Fig.2 of the accompanying drawings	164-66
See Fig.3 of the accompanying drawings	167-69
See Fig.4 of the accompanying drawings	159-60
See Fig.5 of the accompanying drawings	201-03
See Fig.6 of the accompanying drawings	196-98
See Fig.7 of the accompanying drawings	160-61
See Fig.8 of the accompanying drawings	232-34
See Fig.9 of the accompanying drawings	90-94
See Fig.10 of the accompanying drawings	205-7
See Fig. 11 of the accompanying drawings	155-56

The present invention provides a process for preparing the novel chemotherapeutic quinoxaline derivatives of the formula I and their pharmaceutically acceptable salts which comprises reacting 5,8-dimethoxy-2,3-di(4-bromomethyl phenyl) quinoxaline of the formula II shown in the accompanying drawings with compounds of the formula III shown in the accompanying drawings, wherein R_1 and R_2 have the same meaning as described above, in the presence of solvent such as dioxane, tetrahydrofuran or dimethylformamide and at 30-110°C for half an hour to six hours. Reaction mixture on cooling to room temperature is filtered. Filtrate obtained is concentrated and the residue obtained is further purified by column chromatography and/or crystallization.

Compound of the formula II is prepared by reacting compound of the formula IV shown in the accompanying drawings with compound of the formula shown in Fig. 12 of the accompanying drawings by modifying the conditions of C. S. Bajwa et al., J. Med. Chem., 16, 134 (1973). Compound of the formula IV is prepared by following the conditions of B. Krieg [Chem. Ber., 102, 371 (1969)].

Quinoxalines of the formula I and their salts possess valuable chemotherapeutic properties, for example, antiamoebic, antitrichomonad activity.

The following examples illustrate the invention but do not limit the scope thereof.

166761

Example 1

To a solution of 2,3-di(4-bromomethyl phenyl)-5,8-dimethoxy quinoxaline (400 mg) in dioxane (10 ml), was added piperidine (0.37 ml) and the reaction mixture treated to reflux temperature for half an hour. The reaction mixture on cooling was filtered to remove the precipitate and the filtrate was concentrated under vacuum and the residue was dissolved in chloroform. Chloroform solution was washed with water, dried over anhydrous sodium sulphate and concentrated under vacuum. Residue obtained was purified by column chromatography over alumina eluent benzene :ethylacetate (1:1) to obtain pure 2,3-di(4-piperidinomethyl phenyl)-5,8-dimethoxy quinoxaline, which recrystallised from methylene chloride-petroleum ether (60-80°C) mixture, m.p. 159-60°C.

The starting material was prepared as follows :

A mixture of 2,3-dinitro-1,4-dimethoxy benzene (29.8 g), 10% palladium and charcoal (3 g) and glacial acetic acid (400 ml) was shaken under hydrogen at 50 p.s.i. After the completion of reaction, the catalyst was filtered and to the filtrate was added α,α'-dibromomethylbenzil (45 g). The reaction mixture was then heated to 90°C and maintained at that temperature for two and half hours. Excess of acetic acid was distilled off under vacuum and the residue was dissolved in chloroform. Chloroform solution was washed with water and dried over anhydrous sodium sulphate. Concentration of the chloroform extract gave the residue which was purified by chromatography over silica gel, with benzene as eluent to obtain 2,3-di(4-bromomethyl phenyl)-5, 8-dimethoxy quinoxaline (39 g), m.p. 232-35°C.

Example 2

The procedure described in Example 1 was essentially repeated using N-methylpiperazine in place of piperidine to obtain 2,3-di(4-N-methylpiperazinomethyl phenyl)-5,8-dimethoxy quinoxaline in 65% yield, m.p. 160-161°C, [methylenechloride-petroleum ether (60-80°c)].

Example 3

The procedure described in Example 1 was repeated using pyrrolidin in place of piperidine to obtain 2,3-di-(4-pyrrolidinomethyl phenyl)-5, 8-dimethoxy quinoxaline in 78% yield, m.p. 164-66°C [methylene chloride - petroleum ether (60-80°C)].

Example 4

The procedure described in Example 1 was repeated using homopiperidine in place of piperidine to obtain 2,3-di(4-homo-piperidinomethyl phenyl)-5,8-dimethoxy quinoline in 53% yield, m.p. 167-69°C [methylene chloride-petroleum ether (60-80°C)].

Dated this 30th day of March 1987.

(M. A. Jose)
of DePENNING & DePENNING
Agent for the Applicants

166761

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

Section 10

A process for preparing novel chemotherapeutically active 5,8-dimethoxy-2,3-di-(4'-substituted amino-methyl-phenyl) quinoxaline derivatives and pharmaceutically acceptable salts thereof.

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Reclamation, Bombay 400 021,
Maharashtra, India, an Indian
Company.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:-

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The present invention relates to a process for preparing novel chemotherapeutically active 5,8-dimethoxy-2,3-di-(4'-substituted aminomethyl-phenyl)quinoxaline derivatives and pharmaceutically acceptable salts thereof.

The novel 5,8-dimethoxy-2,3-di(4'-substituted amino methyl-phenyl) quinoxaline derivatives of the invention are of the formula I shown in the drawings accompanying the provisional specification, wherein R_1 and R_2 which may be the same or different stand for hydrogen, C_1-C_6 alkyl for example methyl, ethyl or propyl, hydroxy alkyl, for example, hydroxy ethyl, acyl or substituted acyl, for example, acetyl or dichloroacetyl, alkene, for example, allyl; R_1 and R_2 together with the nitrogen to which they are attached form a heterocycle containing one or more hetero atom(s) and is optionally substituted by an alkyl, aralkyl, carboxyalkyl or aryl which is optionally substituted with substituents such as halogen, hydroxy, alkoxy, alkyl or substituted alkyl.

Preferred compounds of the invention are quinoxaline derivatives of the formula I, wherein R_1 and R_2 stand for C_1-C_4 alkyl, for example, methyl, ethyl or isopropyl.

Examples of heterocycle are piperazine, piperidine, pyrrolidine, morpholine or homopiperidine.

Particularly preferred compounds of the invention are the following :

2,3-Di(4-N-methylpiperazinomethyl phenyl)-5,8-dimethoxy quinoxaline.

2,3-Di(4-piperidinomethyl phenyl)-5,8-dimethoxy quinoxaline.

2,3-Di(4-pyrrolidin methyl phenyl)-5,8-dimethoxy quinoxaline.

2,3-Di(4-homopiperidinomethyl phenyl)-5,8-dimethoxy quinoxaline.

Some of the 5,8-dimethoxy-2,3-di(4'-substituted aminomethyl phenyl)-quinoxalines of the invention are listed in the following Table I :

TABLE 1

I: $NR^1R^2 \equiv$

See Fig.1 of the drawings accompanying the provisional specification	m.p. °C
	78-80
$N(C_2H_5)_2 - H_2O$ ①	133-35
$N(CH_2CH=CH_2)_2$	127
$N-COCHCl_2$ CH_2CH_2OH ③ Contd. p. 17) 2	
See Fig.2 of the drawings accompanying the provisional specification	164-66
See Fig.3 of the drawings accompanying the provisional specification	167-69
See Fig.4 of the drawings accompanying the provisional specification	159-60
See Fig.5 of the drawings accompanying the provisional specification	201-03
See Fig.6 of the drawings accompanying the provisional specification	196-98
See Fig.7 of the drawings accompanying the provisional specification	160-61
See Fig.8 of the drawings accompanying the provisional specification	232-34
See Fig.9 of the drawings accompanying the provisional specification	90-94
See Fig.10 of the drawings accompanying the provisional specification	205-7
See Fig.11 of the drawings accompanying the provisional specificati n	155-56

166761

According to the present invention there is provided a process for preparing novel chemotherapeutically active 5,8-dimethoxy-2,3-di-(4'-substituted aminomethyl-phenyl) quinoxaline derivatives of the formula I shown in the drawings accompanying the provisional specification wherein R_1 and R_2 which may be the same or different stand for hydrogen, C_1-C_6 alkyl, for example, methyl, ethyl or propyl, hydroxy alkyl, for example, hydroxy, ethyl, acyl or substituted acyl, for example, acetyl or dichloroacetyl, alkene, for example, allyl; R_1 and R_2 together with the nitrogen to which they are attached form a heterocycle containing one or more hetero atom(s) and is optionally substituted by an alkyl, aralkyl, carboxyalkyl or aryl which is optionally substituted with substituents such as halogen, hydroxy, alkoxy, alkyl or substituted alkyl and their pharmaceutically acceptable salts, which process comprises reacting 5,8-dimethoxy-2,3-di(4-bromomethyl phenyl) quinoxaline of the formula II shown in the drawings accompanying the provisional specification with a compound of the formula III shown in the drawings accompanying the provisional specification, wherein R_1 and R_2 have the above meanings, in the presence of a solvent such as dioxane, tetrahydrofuran or dimethylformamide at 30-110°C, cooling the reaction mixture to room temperature, filtering the reaction mixture, concentrating the filtrate and subjecting the residue to column chromatography and/or crystallization and, if desired, converting the resulting compound of the formula I into its pharmaceutically acceptable salt in a known manner.

The reaction of compound of the formula II with compound of the formula III is carried out for $1/_2$ to 6 hours.

Compound of the formula II is prepared by reacting compound of the formula IV shown in the drawings accompanying the provisional specification with compound of the formula shown in Fig. 12 of the drawings accompanying the provisional specification by modifying the conditions of C.S. Bajwa et al., J. Med Chem., 16, 134 (1973). Compound of the formula IV is prepared by following the conditions of B. Krieg [Chem. Ber., 102, 371 (1969)].

Quinoxalines of the formula I and their pharmaceutically acceptable salts possess valuable chemotherapeutic properties, for example, antiamoebic and antitrichomonad activity.

The following examples illustrate the invention but do not limit the scope thereof :

166761

Example 1

To a solution of 2,3-di(4-bromomethyl phenyl)-5,8-dimethoxy quinoxaline (400 mg) in dioxane (10 ml), was ⑭ added piperidine (0.37 ml) and the reaction mixture treated to reflux temperature for half an hour. The reaction mixture on cooling was filtered to remove the precipitate and the filtrate was concentrated under vacuum and the residue was dissolved in chloroform. Chloroform solution was washed with water, dried over anhydrous sodium sulphate and concentrated under vacuum. Residue obtained was purified by column chromatography over alumina eluent benzene : ethylacetate (1:1) to obtain pure 2,3-di(4-piperidinomethyl phenyl)-5,8-dimethoxy quinoxaline, which recrystallised from methylene chloride-petroleum ether (60-80°C) mixture, m.p. 159-60°C.

The starting material was prepared as follows :

A mixture of 2,3-dinitro-1,4-dimethoxy benzene ⑮ (29.8g), 10% palladium and charcoal (3 g) and glacial acetic acid (400 ml) was shaken under hydrogen at 50 p.s.i. After the completion of the reaction, the catalyst was filtered and to the filtrate was added α,α'-dibromomethylbenzil (45 g). ⑯ The reaction mixture was then heated to 90°C and maintained at that temperature for two and half hours. Excess of acetic acid was distilled off under vacuum and the residue was dissolved in chloroform. Chloroform solution was washed with water and dried over anhydrous sodium sulphate. Concentration of the chloroform extract gave the residue which was purified by chromatography over silica gel, with benzene

166761

as eluent to obtain 2,3-di(4-bromomethyl phenyl)-5, 8-dimethoxy quinoxaline (39 g), m.p. 232-35°C. ⑰

Example 2

The procedure described in Example 1 was essentially ⑰ repeated using N-methylpiperazine in the place of piperidine to obtain 2,3-di(4-N-methylpiperazinomethyl phenyl)-5,8-dimethoxy quinoxaline in 65% yield, m.p. 160-161°C, [methylenechloride-petroleum ether (60-80°C].

Example 3

The procedure described in Example 1 was repeated ⑲ using pyrrolidin in the place of piperidine to obtain 2,3-di-(4-pyrrolidinomethyl phenyl)-5, 8-dimethoxy quinoxalire in 78% yield, m.p. 164-66°C [methylene chloride - petroleum ether (60-80°C].

Example 4

The procedure described in Example 1 was repeated ⑳ using homopiperidine in the place of piperidine to obtain 2,3-di(4-homo-piperidinomethyl phenyl)-5,8-dimethoxy quinoxaline in 53% yield, m.p. 167-69°C [methylene chloride-petroleum ether (60-80°C].

166761

WE CLAIM :

1. A process for preparing novel chemotherapeutically active 5,8-dimethoxy-2,3-di-(4'-substituted aminomethyl-phenyl) quinoxaline derivatives of the formula I shown in the drawings accompanying the provisional specification wherein R_1 and R_2 which may be the same or different stand for hydrogen, C_1-C_6 alkyl, for example, methyl, ethyl or propyl, hydroxy alkyl, for example, hydroxy ethyl, acyl or substituted acyl, for example, acetyl or dichloroacetyl, alkene, for example, allyl; R_1 and R_2 together with the nitrogen to which they are attached form a heterocycle containing one or more hetero atom(s) and is optionally substituted by an alkyl, aralkyl, carboxyalkyl or aryl which is optionally substituted with substituents such as halogen, hydroxy, alkoxy, alkyl or substituted alkyl and their pharmaceutically acceptable salts, which process comprises reacting 5,8-dimethoxy-2,3-di(4-bromomethyl phenyl) quinoxaline of the formula II shown in the drawings accompanying the provisional specification with a compound of the formula III shown in the drawings accompanying the provisional specification, wherein R_1 and R_2 have the above meanings, in the presence of a solvent such as dioxane, tetrahydrofuran or dimethylformamide at 30-110°C, cooling the reaction mixture to room temperature, filtering the reaction mixture, concentrating the filtrate and subjecting the residue to column chromatography and/or crystallization and, if desired, converting the resulting compound of the formula I into its pharmaceutically acceptable salt in a known manner.

2. A process for preparing novel chemotherapeutically active 5,8-dimethoxy-2,3-di-(4'-substituted amino-methyl phenyl

quinoxaline derivatives of the formula I shown in the drawings accompanying the provisional specification wherein R_1 and R_2 are as defined in claim 1 and their pharmaceutically acceptable salts substantially as herein described particularly with reference to Example 1

Dated this 15th day of April 1988.

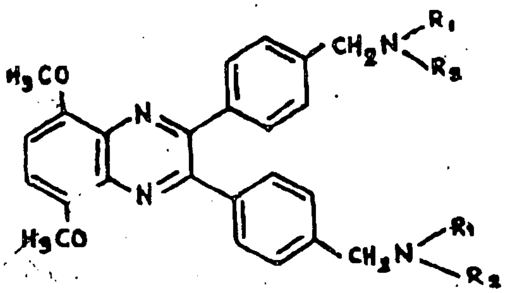
(M. A. JOSE)
of DePENNING & DePENNING
Agent for the Applicants

2 SHEETS
SHEET 1

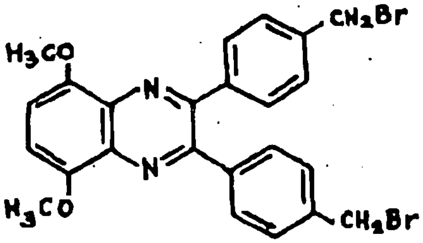
HOECHST INDIA LIMITED

No. ~~1256/BOM/87~~ 166761

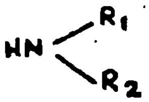
PROVISIONAL SPECIFICATION



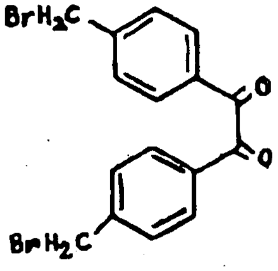
FORMULA I



FORMULA II



FORMULA III



FORMULA IV

(M. A. JOSE)
OF DEPENNING & DEPENNING
AGENT FOR THE APPLICANTS

2 SHEETS
SHEET 2

HOECHST INDIA LIMITED

No. ~~185/Bom/87~~ 166761

PROVISIONAL SPECIFICATION

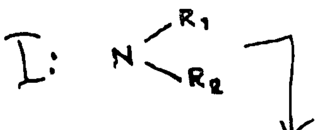


FIG. 1

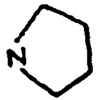


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FIG. 2

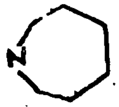

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FIG. 3

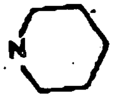

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FIG. 4

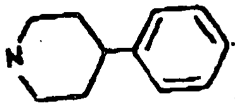

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FIG. 5

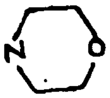

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FIG. 6

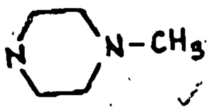

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FIG. 7

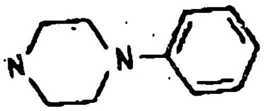

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FIG. 8

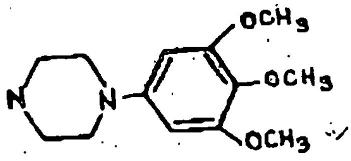

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FIG. 9

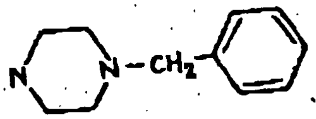

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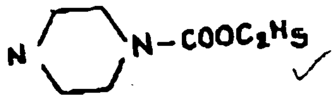
FIG. 10



⑬

FIG. 11

(cont'd. p. 12)

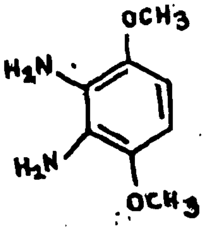


FIG. 12

(M. A. JOSE)
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AGENT FOR THE APPLICANTS